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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,642	07/16/2003	Krisztina M. Zsebo	01017/33718B	9682

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,642	ZSEBO ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 16 July 2003 has been entered in full. Claims 1-70 are cancelled and claims 71-90 are added.

Claims 71-90 are under consideration in the instant application.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. *Specifically, the claims recite figure numbers rather than sequence identifiers.* Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Specification

2. The disclosure is objected to because of the following informalities:

2a. An updated status of the parent nonprovisional applications should be included in the first sentence of the specification.

2b. The cross-reference identification to related parent nonprovisional applications at the first line of the specification or application data sheet should be corrected. According to PTO records, Application No. 08/486,546, filed May 25, 1995 is a divisional application (and not a continuation-in-part) of Application No. 08/172,329, filed December 21, 1993.

2c. The filing date of the parent nonprovisional application 09/635,249 should be corrected in the first line of the specification or application data sheet. According to PTO records, the filing date of the '249 application is 8/7/2000. However, the application data sheet and

amendment to the first line of the specification submitted 16 July 2003 indicate that the '249 application was filed 8/9/2000.

2d. The specification is replete with references to U.S. patent Application Nos. The specification should include an updated status of these applications. For example, see pg 24, line 23 and pg 182, line 25.

2e. The Brief Description of the Drawings fails to refer to Figures 24A-24B; Figures 29A-29B; Figures 30A-30B; Figures 42A-42D; Figures 44A-44C; Figures 56A-56B.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 71-90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 71-90 are directed to a method of stimulating growth of stromal cells in a human comprising administering to the human an effective amount of a human stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier. The claims recite that the SCF polypeptide is selected from the group consisting of amino acids 1-162, 1-164, and 1-165 as set out in Figure 15C. The claims recite that the SCF polypeptide consists of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164,

2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 as set out in Figure 42A-C. The claims recite that the SCF polypeptide is selected from the group consisting of amino acids 1-152, 1-157, 1-160, 1-161, and 1-220 as set out in Figure 44A-C. Additionally, the claims recite that the stem cell factor is co-administered with at least one or more cytokines selected from a group consisting of IL-1, IL-2, Il-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF. The claims recite that the pharmaceutically acceptable carrier is suitable for topical delivery, oral delivery, parenteral delivery, pulmonary delivery, and nasal delivery.

The specification teaches several experiments in which mice, rats, baboons, and dogs are intravenously or subcutaneously administered SCF alone or SCF in combination with other cytokines (pg 105-110, 151-168). The peripheral blood and bone marrow removed from the subjects is monitored for such cells as red blood cells, platelets, and white blood cells. The specification also teaches that the effect of SCF on survival of mice after lethal irradiation is measured. At pg 177, the specification discloses that human bone marrow is cultured on transduced stromal cells. However, while the relevant literature teaches that stromal cells *produce* stem cell factor (see pg 177, lines 14-15; Huang et al., Cell 63: 225, 1990; Zsebo et al., Cell 63: 213, 1990; Williams et al., Cell 63: 167, 1990), the specification does not teach any methods or working examples that stimulate the growth of stromal cells *in vitro* or in any subject, particularly a human, by administration of SCF alone or in combination with a cytokine. Although the experiments in the specification monitor the numbers of numerous cell types, stromal cells are not one of the cells examined. Furthermore, the skilled artisan would not be able to predict the effects of administration of a SCF polypeptide or SCF-cytokine composition

since it cannot be determined from the specification of the instant application or the claims which stromal cells are being targeted for the stimulation of growth. Stromal cells are present for example, in the bone marrow, thymus, endometrium (see for instance, Derubeis et al. Ann Biomed Engineer 32(1): 160-164, 2004; Anderson et al. Annu Rev Immunol 14: 73-99, 1996; Irwin et al. Endocrinol 129(5) : 2385-2392, 1991). Post-filing date references also disclose that stromal cells in these environments are heterogeneous cell populations, with different growth rates, morphologies, and markers (Bianco et al., Stem Cells 19: 180-192, 2001, pg 181; Screpanti et al., J Cell Sci 105: 601-606, 1993, pg 603-604). Therefore, undue experimentation would be required of one skilled in the art to determine the efficacy of growth of stromal cells in a subject by administration of a SCF or a SCF-cytokine composition. A large quantity of experimentation would also be necessary to determine the target stromal cells, optimal administration route, dosage, frequency, and duration of the treatment.

Additionally, relevant literature reports that the goal of delivering proteins and peptides noninvasively has only achieved modest success, with poor applicability to proteins and peptides (pg 343, col 1-2; Pettit et al. Trends Biotechnol 16: 343-349, 1998). The problems posed by proteins and peptides is their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, limited success has been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical instability (pg 344-345). Much effort has been given to the

transdermal delivery of pharmaceutical products, but clinical applications have been limited to non-protein drugs because of the skin's poor permeability to proteins and peptides (pg 343, col 2). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Although the pulmonary delivery route has generated the most encouraging data, the bioavailability of proteins (i.e. the amount of protein that crosses from the alveoli in to the pulmonary circulation) is dependent on the physical characteristics of the delivered protein and is not the same for proteins and peptides in general (pg 343-344). Therefore, the state of the prior art establishes the unpredictability of delivering proteins to a subject.

Furthermore, undue experimentation would be required of the skilled artisan to administer all possible SCF fragments recited in the claims to a subject and determine the growth of stromal cells. Undue experimentation would also be required of the skilled artisan to administer all possible combinations of SCF fragments with one or more cytokines to a human and determine the growth of stromal cells. Regarding the numerous SCF polypeptide fragments, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These

regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. The specification of the instant application only teaches that the human SCF polypeptide, particularly fragments comprising amino acids 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-162, 1-163, 1-164, 1-165, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 of SEQ ID NOs: 46, 61, and 63 enhance the proliferation and differentiation of bone marrow progenitor cells (pg 108-114, 170-178, 185). The specification does not teach that these fragments stimulate the growth of stromal cells in a human. The specification does not disclose any methods or working examples to demonstrate a human SCF polypeptide comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, as set out in Figures 42A-C and 44A-C or any other variant SCF polypeptides have any specific activity. A large quantity of experimentation would be required of the skilled artisan to determine any structural or functional characteristics of all possible SCF polypeptides, including the SCF polypeptides comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127 of SEQ ID NOs: 46, 61, and 63. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate SCF polypeptides that stimulate growth of stromal cells and to determine the efficacy of treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of protein administration to a subject, and the breadth of the claims which fail to recite any specific location of the targeted stromal cells (i.e., bone marrow, thymus, endometrium, etc.) targeted for growth stimulation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 78 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 78 and 80, the acronyms "IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
14 April 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER